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22/Appeal Brief (3)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Lisbeth Illum

Serial No.: 08/359,937 Group Art Unit: 1502

Filed: December 20, 1994 Examiner: G. Kishore

For: *SMALL PARTICLE COMPOSITIONS FOR INTRANASAL DRUG DELIVERY*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-28 in the Office Action mailed December 29, 1995, and maintained in the Advisory Action mailed April 16, 1996, in the above-identified patent application. A Notice of Appeal was mailed to the U.S. Patent Office on April 29, 1996. A check in the amount of $290.00 for the filing of the Appeal Brief is enclosed.

I. Real Party in Interest

The real parties in interest of this application are DanBiosyst and The West Company.

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II. Related Appeals and Interferences

There are no related appeals or interferences known to Appellant, the undersigned, or Appellant's assignee which directly effect, which would be directly effected by, or which would have a bearing on the Board's decision in this appeal.

III. Status of Claims

Claims 1-28 are pending. Claims 1-10 and 15-16 stand rejected under the judicially created doctrine of obviousness-type double patenting. Claims 11-14 and 17-28 stand rejected under the judicially created doctrine of non-statutory double patenting. Claims 1-5, 11 and 13 stand rejected under 35 U.S.C. § 102(e). Claims 1-28 stand rejected under 35 U.S.C. §103. The text of the claims on appeal as amended is set forth in the attached Appendix A.

IV. Status of Amendments

An Office Action was mailed from the U.S. Patent Office on December 29, 1995, in which claims 1-28 were finally rejected. Appellants mailed an Amendment in response to the Office Action on March 29, 1996. The Examiner mailed an Advisory Action on April 16, 1996 indicating that the Amendment mailed March 29, 1996 would be entered.

V. Summary of the Invention.

The claims are directed to a particulate drug delivery composition which includes bioadhesive microspheres and a systemically active drug, wherein at least 90 wt % of the microspheres have a diameter of between 0.1 μm and 10 μm, and the composition is suitable for administration to a mammal intranasally for systemic delivery of a therapeutically effective amount of the drug. The microspheres can be formed of a protein, synthetic polymer or starch (claims 3, 4, 15, 16), stabilized by crosslinking (claim 5) or heating (claim 6) or a material that gels in contact with the mucosa (claim 2). The composition can include an absorption enhancer, such as a surfactant (claims 7, 8). Suitable drugs include biologically active peptides such as insulin and calcitonin (claims 9, 10). The narrow size distribution of the microspheres facilitates administration in powder administration devices such as insufflators (claim 12) and results in a more uniform dose of the active drug.

Claims are also directed to a method of systemic drug delivery by administration of the compositions of claims 1-10 (claims 17-28), a method for intranasal administration using the system of claim 11 (claim 13), and a method for treating a patient with diabetes with the composition of claim 10 (claim 14).

VI. Issues on Appeal

The issues on appeal are:

(1) whether claims 1-10 and 15-16 should be rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-13 of U.S. Patent No. 5,204,108 to Illum;

(2) whether claims 11-14 and 17-28 should be rejected under the judicially created doctrine of double patenting over U.S. Patent No. 5,204,108 to Illum;

(3) whether claims 1-5, 11 and 13 should be rejected under 35 U.S.C. § 102(e) in view of U.S. Patent No. 4,847,091 to Illum ("Illum");

(4) whether claims 1-28 should be rejected under 35 U.S.C. § 103 as obvious over Illum, L., *Nato ASI Symposium*, 125:205-210 (1986) "(Illum (1986))"; and

(5) whether claims 7-12, 14 and 23-36 should be rejected under 35 U.S.C. § 103 over Illum or Illum (1986), in view of Hanson *et al.*, *Advanced Delivery Systems for Peptides and Proteins*, p. 233-242 (1988) ("Hanson"), or Salzman *et al.*, *New Eng. J. Med.*, 312:1078-1084 (1985) ("Salzman"), or vice versa.

VII. Grouping of the Claims.

Claims 1-28 stand or fall separately. Claims 1-6 and 15-16 are directed to a particulate drug delivery composition for intranasal delivery which includes bioadhesive microspheres and a systemically active drug, wherein at least 90 wt % of the microspheres of the composition have a diameter of between 0.1 μm and 10 μm, and wherein the composition is capable of systemic delivery of a therapeutically effective amount of the drug to a mammal upon intranasal administration. Claims 7-8

are directed to the composition of claim 1 further including an absorption enhancer. Claims 9-10 are directed to the embodiment wherein the drug is a biologically active peptide. Claims 2, 3, 4, 5, 6, 15, and 16 are directed to microspheres formed of specific materials.

Claims 11-12 are directed to a system for intranasal drug delivery which includes the drug delivery composition of claim 1 and a container having an orifice through which the composition can be delivered to the nasal mucosa in a gas stream. Claims 13-14 are directed to a method wherein the composition of claim 1 is introduced in a gas stream into the nose.

Claims 17-22 and 27-28 are directed to a method for systemically delivering an active drug to a mammal, wherein a composition including bioadhesive microspheres and an active drug, wherein at least 90 wt % of the microspheres of the composition have a diameter between 0.1 μm and 10 μm, is administered intranasally to systemically deliver a therapeutically effective amount of the drug to the mammal. Claims 23 and 24 are directed to the embodiment of claim 17 wherein the composition further includes an absorption enhancer. Claims 25 and 26 are directed to the method of claim 17 wherein the drug is a biologically active peptide.

VIII. Argument

1. <u>The obviousness-type double patenting rejection over U.S. Patent No. 5,204,108 should be withdrawn.</u>

Claims 1-10 and 15-16 were rejected under the doctrine of obviousness-type double patenting as obvious over claims 1-13 of U.S. Patent No. 5,204,108 to Illum.

a. U.S. Patent No. 5,204,108 to Illum

Claims 1-13 of U.S. Patent No. 5,204,108 are directed to drug delivery compositions suitable for transmucosal delivery, which are substantially free of enhancer, and which include microspheres made of starch, gelatin, collagen or dextran, and a bioactive peptide having a maximum molecular weight of 6000 suitable for systemic administration. Claim 2 defines the microspheres as having a diameter between 10 and 100 microns. Claim 3 requires the microsphere material to be cross-linked; claim 4 defines the microspheres as formed from the drug. Claim 5 is limited to microspheres suitable for administration to the vagina; claim 6 is limited to microspheres suitable for administration to the eye; claim 7 is limited to microspheres suitable for delivery to the nasal mucosa. Claim 9 defines the peptide as having a molecular weight of at least 1000; claim 10 defines the peptide as insulin or calcitonin. Claims 11, 12 and 13 define the microspheres as having drug incorporated therein.

b. Claims 1-10 and 15-16 of the present application

Claims 1-10 and 15-16 of the present application are limited to microspheres of between 0.01 and 10 microns in diameter. Disregarding all other limitations, there is no disclosure in the claims (or for that matter, the specification) of the '108 patent

to Illum that would lead one of ordinary skill in the art to select microspheres of 1/10th to 1/100th of the size of the microspheres of the '108 patent. As discussed in more detail below, unexpectedly better systemic delivery was obtained following nasal administration of the claimed microspheres than was obtained with with larger diameter microspheres.

c. The rejection does not meet the legal criteria defined by the courts

The Federal Circuit has held that the mere fact that a broad process claim of the patent reads on or dominates a narrower claim does not, per se, justify a double patenting rejection, and that in the double patenting rejection, the specification of the patent should not be used as prior art. *In re Kaplan*, 789 F.2d 1574, 229 USPQ 678 (Fed. Cir. 1986).

Obviousness-type double patenting rejections are made when a U.S. patent application by an inventor claims an obvious variation of the invention claimed in another U.S. application or issued U.S. Patent by the same inventor. The function of the rejection is to prevent an inventor from obtaining more than one patent for the same invention. A proper rejection must consider all limitations of the claims. However, the specification of the issued patent cannot be used as prior art. A rejection for "obviousness-type" double patenting should only be made when there is no "patentable difference" between the claims of the application at issue and the

claims of the other application or patent. "[A] double patenting of the obviousness type rejection is "analogous to [a failure to meet] the non-obviousness requirement of 35 U.S.C. §103, except that the patent principally underlying the double patenting rejection is not considered prior art." In re Longi, 759 F.2d 887, 892, n. 4. (Fed. Cir. 1985), *citing* In re Braithwaite, 379 F.2d 594, 600, n. 4 (C.C.P.A. 1967). It is a judicially-created doctrine. General Foods v. Studiengesellschaft Kohle MbH, 972 F.2d 1272, 1278-1279 (Fed. Cir. 1992); In re Braat, 937 F.2d 589, 592 (Fed. Cir. 1991).

A proper double patenting rejection must consider the claim as a whole, including all limitations. General Foods, at p. 1278; Carman v. Wahl, 724 F.2d 932, 940 (Fed. Cir. 1983); *cf.* Ex Parte Crissy, 201 U.S.P.Q. (BNA) 689, 693 (P.O.B.A. 1976). As discussed by the Court in General Foods at 1278, the proper analysis for double patenting is to first determine if the same invention is being claimed twice; if not, then the question is whether or not the rejected claims are patentably distinct from the claims in the patent.

The standard for obviousness with respect to double patenting is the same as that under 35 U.S.C. §103: whether the prior art, as a whole, would lead one of ordinary skill in the art to make and use that which is claimed. The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177

(C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art (in this case, the claims in the '108 patent) suggests the claimed invention; and (ii) the prior art (the claims in the '108 patent) indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

The examiner has cited no art supplemental to the claims that demonstrate that those skilled in the art would be led to substitute microspheres of 1/10th to 1/100th of the size of the microspheres of the '108 patent to Illum, with any expectation of success in systemic drug delivery. In fact, one would be inclined to think that larger, rather than smaller, would achieve greater delivery. Accordingly, the rejection of claims 1-10 and 15-16 under the doctrine of obviousness-type double patenting over claims 1-13 of the '108 patent to Illum should not be sustained.

2. The double patenting rejection over U.S. Patent No. 5,204,108 should be withdrawn.

Claims 11-14 and 17-28 were rejected under the judicially created doctrine of double patenting, presumably over some claims of U.S. Patent No. 5,204,108 to Illum, although the examiner's comments indicate that the rejection may have been made on the basis of the disclosure of the patent.

The '108 patent to Illum is discussed above.

a. Claims 11-14 and 17-28 of the present application

Claims 11-14 and 17-28 are directed to a system for intranasal administration (claims 11 and 12) and method for intranasal delivery (claims 14 and 17-28). The claims all require the same limitations as claim 1: that the microspheres have a diameter of between 0.1 and 10 microns. The claims are further limited to intranasal delivery, and even more limited in the case of claims 12 and 13 to the use of a container delivering the particles via a gas stream.

b. The rejection does not meet the legal criteria defined by the courts

A double patenting rejection requires that the claims be directed to the same subject matter. Double patenting requires an analysis similar to that for an obviousness-type double patenting rejection, as discussed in section 1, but for novelty rather than non-obviousness, using the same criteria as an analysis under 35 U.S.C. §102. The examiner has completely failed in making such an analysis, improperly using the specification as the basis for a double patenting rejection, when the claims of the present application are directed to methods of intranasal administration and the claims of the '108 patent are directed to compositions for delivery to a mucosal surface. See MPEP §804.02 describing non-statutory double patenting as "where an application claims an invention which is not patentably distinct from an invention claimed in a commonly owned patent with the same or a different inventive entity."

The claims of the present application define a different invention from the claims of the '108 patent to Illum: a method whereby microspheres having a diameter of between 0.1 and 10 microns are administered intranasally to achieve systemic delivery of a drug, which does not require the inclusion of an enhancer

No art has been cited that demonstrates that the claims of the '108 patent to Illum, directed to large microspheres for delivery to a variety of mucosal surfaces, including vaginal and ophthalmic surfaces, which have as an essential element the inclusion of a permeation enhancer, would be considered the same as, or even equivalent to, the claims directed to a method for intranasal delivery of very small microspheres which do not have to include an enhancer. Accordingly, the claims are not directed to the same patentably indistinct subject matter.

3. The claimed compositions and methods are not disclosed in Illum.

Claims 1-5, 11 and 13 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 4,847,091 to Illum.

a. U.S. Patent No. 4,847,091 to Illum.

Illum discloses microspheres incorporating sodium cromoglycate which are formed of a material having ion exchange properties. The disclosure of Illum is limited to the synthesis of microspheres incorporating sodium cromoglycate and the use of the microspheres for local treatment. Illum discloses that the microspheres can be used for treatment of allergic conditions. For example, Illum discloses treatment

of conditions of the outer eye such as hay fever or conjunctivitis (col. 3, lines 3-20), conditions of the nose such as perennial rhinitis, and conditions of the lung such as asthma. The disclosure of Illum thus is limited to the administration of microspheres for localized treatment of a condition.

b. Nothing in Illum provides any disclosure or suggestion of the compositions claimed by the Appellant.

Nothing in Illum teaches or suggests that microspheres can be formed which are capable of systemic delivery of a therapeutically effective amount of a drug upon nasal administration. Nothing in Illum suggests microspheres limited to a diameter of between 0.1 and 10 microns. Rather, Illum teaches away from systemic delivery by suggesting the use of the sodium cromoglycate containing microspheres for local treatment of conditions in the eye, nose and lung, such as allergic conditions (col. 3, lines 3-38).

Nothing in Illum suggests a composition including microspheres and an active drug which can be administered intranasally to systemically deliver a therapeutically effective amount of the drug. As noted in the Appellant's Supplemental Response mailed May 26, 1994, in the parent of the above-identified application, sodium cromoglycate is poorly absorbed and not useful for systemic treatment. Rather, sodium cromoglycate is used therapeutically for local treatment. As indicated in the Supplemental Response mailed May 26, 1994, and in the documents cofiled therewith,

sodium cromoglycate is poorly absorbed from the gastrointestinal tract and is consequently used for local action. It is used for the treatment of asthma, rhinitis and nasal congestion, which are clearly localized therapeutic treatment applications. Nothing in Illum suggests or teaches systemic delivery of a drug using the microspheres. Illum instead teaches away from systemic delivery by suggesting only local administration.

Nothing in the disclosure of Illum suggests that the microspheres are capable of systemic delivery of a drug. Nothing in Illum suggests that intranasally administered sodium cromoglycate penetrates nasal tissue and enters the body and is capable of causing a systemic therapeutic effect. Rather, as indicated in Appellant's Supplemental Response mailed May 26, 1994, sodium cromoglycate is known to those skilled in the art to be poorly absorbed and is therapeutically administered topically for local action.

c. The rejection does not meet the legal criteria defined by the courts

The claims have been improperly rejected under 35 U.S.C. §102(e). §102(e) reads as follows:

> the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, . . (emphasis added)

The present application is by Lisbeth Illum. The '091 patent is to Lisbeth Illum. Therefore the patent is not by another.

However, even if the rejection were made under 35 U.S.C. §102(b), in order for a rejection under 35 U.S.C. § 102 to be proper, all of the material elements of the claims must be present in one prior art source. *In re Marshall* (CCPA 1978) 577 F2d 301.

The '091 patent fails to disclose, and in fact teaches away, the claimed compositions because (1) the '091 requires the inclusion of sodium cromoglycate and the claimed compositions do not; (2) sodium cromoglycate is useful for local, not systemic delivery of compounds, an essential characteristic of the claimed compositions; and (3) there is no disclosure in the '091 patent of the claimed size range, an essential characteristic of the claimed compositions.

The Appellant has provided evidence including literature articles, in Appellant's Supplemental Response mailed May 26, 1994, indicating that sodium cromoglycate is known to those skilled in the art to be poorly absorbed and to be therapeutically effective when administered topically for local action. For example, Katzung, Bertram G., "Basic & Clinical Pharmacology," Lange Medical Publications, Los Altos, CA 94022, 1984, states on page 228 that "cromolyn is poorly absorbed from the gastrointestinal tract. For use in asthma, it must be applied topically," and states on page 230 that "because it is so poorly absorbed, adverse effects of cromolyn

are minor and are localized in the sites of deposition." Similarly, Martindale (*Extra Pharmacopoeia*, Vol. 30, p. 1142) also enclosed with Appellant's Supplemental Response mailed May 26, 1994 states that sodium cromoglycate is "poorly absorbed" and that "less than 7% of an intranasal dose is absorbed".

Thus, nothing in the '091 patent to Illum, or in the literature in the area of drug delivery, indicates that the compositions disclosed by Illum, including microspheres and sodium cromoglycate, could be administered intranasally to systemically deliver a therapeutically effective amount of a drug. There is no indication that there is systemic delivery with the Illum compositions, much less that there is systemic delivery of a therapeutically effective amount of a drug.

In contrast, the Appellant has demonstrated the synthesis and use of compositions including microspheres which are capable of systemic delivery of a therapeutically effective amount of a drug in a mammal. The Appellant further has provided experimental results which show that the compositions are therapeutically effective systemically. For example, the compositions were intranasally administered to systemically deliver insulin to sheep in a therapeutically effective amount to reduce plasma glucose (see Example 3 and page 26 of the specification).

In summary, the '091 patent does not disclose the claimed compositions, as required for a proper rejection under 35 U.S.C. § 102. *In re Arkley et al.*, 172 USPQ 524, 526 (CCPA, 1972). In order for prior art to anticipate a claimed

compound on the ground that it is inherently produced in the prior art process, the inherency must be certain. *Ex parte Cyba* (POBA 1966) 155 USPQ 756; *Ex parte McQueen* (POBA 1958) 123 USPQ 37. Even the fact that a prior art article may inherently have the characteristics of the claimed product is not sufficient. *Ex parte Skinner* (BPAI 1986) 2 PQ2d 1788. Here, however, the differences are clear in composition and in effect, therefore rendering the claimed compositions distinct from those of the '091 patent to Illum both chemically as well as functionally.

4. The claimed compositions and methods are not obvious in view of Illum (1986).

Claims 1-28 stand rejected under 35 U.S.C. § 103 as obvious over Illum, L., *Nato ASI Symposium*, 125:205-210 (1986) ("Illum (1986)").

a. Illum (1986).

Illum (1986) discloses the fabrication of microspheres which are bioadhesive in order to increase time of contact with the nasal mucosa. Illum discloses that the preferred size range of the microspheres is 40-60 μm (page 207). Illum also discloses that the microspheres swell to form a mucoadhesive system that is cleared very slowly from the nose.

b. Illum (1986) does not disclose or suggest the drug delivery compositions or methods for their administration claimed.

Illum (1986) discloses albumin, starch and DEAE-dextran microspheres for use in nasal administration, and that the preferred size range of the microspheres is

40-60 μm (page 207). Illum (1986) does not teach or suggest the use of microspheres having a diameter less than 20 μm for use in intranasal delivery. Nothing in Illum (1986) would have motivated one of ordinary skill in the art to make or use the claimed drug delivery systems including microspheres having a diameter between 0.1 μm and 10 μm. In view of Illum (1986), one of ordinary skill in the art would not have been motivated to make or use the claimed drug delivery systems for improved systemic delivery of an active drug after nasal administration.

The Appellant has demonstrated that, unexpectedly, improved systemic therapeutic results are obtained by intranasal administration of microspheres having a diameter less than 10 μm (see Example 1 of the specification), which is not suggested in the cited art. All of the microspheres disclosed in Illum (1986) have a size greater than 10 μm. For example, the albumin microspheres disclosed in Illum (1986) have a swelled size of 40 μm or greater, and since the degree of swelling is 40%, this corresponds to a size of 28 μm or greater at the time of application. The starch microspheres disclosed in Illum (1986) have a dry volume mean diameter of approximately 20 μm, while the DEAE dextran microspheres obtained from Pharmacia disclosed in Illum (1986) have a quoted dry bead size ranging from 25 to 125 μm. Thus, nothing in Illum (1986) discloses or suggests making or using microparticles having a diameter between 0.1 and 10 μm. There is no suggestion in

Illum (1986) of the advantages and features of the use of lower diameter microspheres demonstrated by the Appellant.

c. The rejection does not meet the legal criteria defined by the courts

In view of Illum (1986), one of ordinary skill would have had no motivation to practice the claimed methods or make the claimed compositions including microspheres having a size between about 0.1 and 10 μm to improve intranasal systemic absorption of a drug. Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. *In re Vaeck* (CAFC 1991) 947 F.2d 488, 20 PQ2d 1438. In the absence of hindsight, there is no suggestion in Illum (1986) of the methods and compositions claimed. In deciding obviousness one must look at prior art from the vantage point in time prior to when the invention was made; hindsight obviousness after the invention has been made is not the test. *In re Carroll* (CCPA 1979) 601 F.2d 1184, 202 USPQ 571. In the absence of hindsight, there is no suggestion in either Illum or Illum (1986) of the compositions or methods for their administration claimed.

5. The claimed methods and compositions are not obvious in view of Illum or Illum (1986), alone or in view of Hanson or Salzman.

Claims 7-12, 14 and 23-36 stand rejected under 35 U.S.C. § 103 as being obvious over the '091 patent to Illum or Illum (1986) in view of Hanson *et al.*,

Advanced Delivery Systems for Peptides and Proteins, p. 233-242 (1988) ("Hanson"), or Salzman *et al.*, *New Eng. J. Med.*, 312:1078-1084 (1985) ("Salzman"), or vice versa.

a. The disclosure of the '091 patent to Illum and Illum (1986).

As discussed in detail above, nothing in the '091 patent to Illum or Illum (1986) teaches or suggests the methods and compositions recited in the amended claims.

The '091 patent to Illum does not provide any teaching of, or motivation for, making microspheres for systemic delivery of a therapeutically effective amount of a drug, or for administering such compositions intranasally to produce a systemic therapeutic effect. The '091 patent to Illum discloses the preparation of microspheres incorporating sodium cromoglycate for local treatment of conditions such as allergic conditions of the eye and nose. Nothing in the '091 patent to Illum suggests that a systemic effect is obtained after administering the microspheres.

Illum (1986) does not disclose a drug delivery system including microspheres having the features recited in the claims. Illum (1986) discloses the preparation of a variety of different microspheres, none of which have a size less than ten microns. Illum (1986) does not disclose or suggest making or administering the drug delivery formulations including microspheres having a diameter between 0.1 and 10 microns defined by the claims. Illum (1986) further does not provide any demonstration that

the microspheres are capable of systemic delivery of a therapeutically effective amount of an active drug after nasal administration.

b. The disclosure of Hanson and Salzman.

Hanson is a study of the intranasal delivery of the peptide, salmon calcitonin. Hanson discloses that the biological response to nasal administration of calcitonin can be increased by the addition of various surfactants, including cationic, nonionic, amphoteric and anionic surfactants.

Salzman discloses that intranasal administration of aerosolized insulin in combination with the surfactant laureth-9 increases absorption of the insulin across the nasal mucosa. Salzman also discloses that the insulin in combination with the surfactant was effective in diminishing postprandial hyperglycemia in Type I diabetes in patients.

Neither Hanson or Salzman suggests a drug delivery system including microspheres. Nothing in Hanson or Salzman suggests the selection of a drug delivery composition including microspheres having a diameter between 0.1 to 10 μm for the intranasal administration and systemic delivery of a drug. In view of Hanson and Salzman, there would have been no motivation for one of ordinary skill in the art to make or to administer the claimed compositions.

c. In combination, Illum, Illum (1986), Hanson, and Salzman do not disclose or suggest the compositions and methods claimed.

The '091 patent to Illum and/or Illum (1986), alone or in combination with Hanson and Salzman do not teach or suggest the claimed drug delivery compositions, and methods for their administration to systemically deliver a therapeutically effective amount of a drug. In view of the combined teachings of the applied art, there is no suggestion of the compositions and methods defined by the limitations of the claims.

Nothing in the applied art suggests the claimed particulate drug delivery compositions, including microspheres, wherein at least 90 wt% of the microspheres have a diameter between 0.1 and 10 μm, and an active drug, which can be intranasally administered to systemically deliver a therapeutically effective amount of the drug to a mammal, and wherein improved systemic delivery is obtained in comparison to the use of larger particles. Nothing in the applied art alone or in combination suggests the particular embodiments defined by the claims, wherein, for example, the microspheres are prepared from a material that will gel in contact with the mucosal surface (claims 2 and 18), or wherein the microspheres are formed from starch (claims 4 and 20) or certain modified starches (claims 16 and 28). The applied art also does not teach or suggest the embodiments of claims 9-10 and 25-26, wherein the drug delivery composition includes microspheres and a biologically active peptide

such as insulin or calcitonin, and is capable of systemic delivery of a therapeutically active amount of the peptide upon intranasal administration.

In order to make a determination of obviousness under 35 U.S.C. § 103, the prior art, viewed by itself and not in retrospect, must suggest doing what the applicant has done. *In re Shaffer* (CCPA 1956) 229 F.2d 476, 108 USPQ 326; *In re Skoll* (CCPA 1975) 523 F.2d 1392, 187 USPQ 481. The applied art, alone or in combination, does not suggest the compositions or methods defined by the precise limitations of the claims.

d. There would have been no motivation to make the claimed compositions or to practice the claimed methods in view of Illum, Illum (1986), Hanson or Salzman, alone or in combination.

In view of the applied art and knowledge available in the art, there would have been no motivation to make the compositions for systemic delivery of drugs recited by the claims. There is no suggestion in the applied art of providing a drug delivery composition including microspheres and an active drug, wherein at least 90 wt % of the microspheres of the composition have a diameter between 0.1 μm and 10 μm, and wherein the composition is capable of delivering systemically a therapeutically effective amount of the drug upon intranasal administration. There further would have been no motivation to provide the different embodiments claimed, wherein, for example, the microspheres are heat stabilized, include an absorption enhancer, or

include a biologically active peptide such as insulin or calcitonin. In view of the applied art, one of ordinary skill in the art would not have been motivated to practice the claimed methods or make the claimed compositions, or to expect that they would be effective for systemic delivery of drug upon nasal administration. A valid rejection under 35 U.S.C. § 103 must be based on prior art that indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469 (Fed. Cir. 1988).

The teachings of the applied art and knowledge available in the art would have lead one of ordinary skill away from practicing the claimed methods and making the claimed compositions. One of ordinary skill in the art would not expect that a drug delivery composition including microspheres having a diameter between 0.1 μm and 10 μm could be used for improved systemic delivery of a therapeutically effective amount of an active drug such as a peptide. As indicated in Gizurarson, *Advanced Drug Delivery Reviews*, Vol. 11, 1993, pp. 331, attached as Exhibit A with Appellant's Amendment mailed March 29, 1996, nasal administration and systemic delivery of protein drugs in a therapeutically effective amount has proved difficult. Gizurarson states that the absorption and delivery of peptides without adversely effecting the physiology of the nose has proved difficult because absorption of peptide drugs across the nasal mucosa is difficult. There is no motivation in the applied art to make a drug delivery system including microspheres having a diameter of between

0.1 to 10 μm for systemic delivery of a drug via nasal administration. The applied art and knowledge available in the art would not have lead or motivated one of ordinary skill in the art to practice the methods or make the compositions defined by the claims.

e. The unexpected results demonstrated by the Applicant are not obvious in view of Illum, Illum (1986), Hanson and Salzman.

Nothing in the combined applied art suggests the unexpected results demonstrated by the Appellant. The Appellant has provided data demonstrating that the use of microspheres in a drug delivery system having a diameter between 0.1 μm and 10 μm permits improved absorption and systemic delivery of an active drug after nasal administration, in comparison to prior art drug delivery systems using larger diameter microspheres. The applied art does not suggest the improved results obtained using the claimed drug delivery systems.

Example 1 of the above-identified application provides a comparison of the results of intranasal administration of insulin in starch microspheres of diameter greater than 10 μm and less than 10 μm, which shows that a significant increase in blood insulin concentration was obtained using the smaller (less than 10 μm) microspheres. Example 2 demonstrates that microspheres of 1 to 10 μm have a much longer residence time in the nasal cavity than microspheres of 40 μm. Example 3 shows that improved intranasal absorption of insulin in sheep was obtained using

small (less than 10 μm) hyaluronic acid and hyaluronic acid-dextran microspheres compared to larger microspheres (25 μm) of starch. Appellant provided additional data, attached as Exhibit 15 to the Amendment mailed March 21, 1994, in the parent application, demonstrating that the absorption of granulocyte-colony stimulating factor was enhanced using microspheres of 1-10 μm diameter in comparison to larger microspheres.

f. Summary

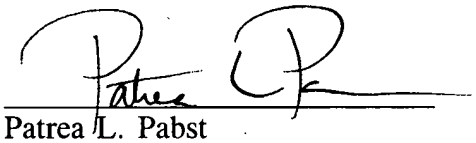
In summary, in order to make a determination of obviousness under 35 U.S.C. § 103, the prior art must suggest the claimed invention. *In re Dow Chemical Company*, 837 F.2d 469 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686 (Fed. Cir. 1987). Nothing in Illum, Illum (1986), Hanson or Salzman, alone or in combination, provides any suggestion of the claimed compositions including microspheres, or provides any teaching of methods for making or using the compositions, or any suggestion that they would provide the beneficial effects shown by the Appellant.

IX. Summary and Conclusion

Appellant submits that the claim: should not be rejected for either obviousness-type double patenting nor double patenting in view of the claims of U.S. Patent No. 5,204,108 to Illum; are novel under §102 over the disclosure of U.S. Patent No. 4,487,091 to Illum; and are not obvious under §103 in view of the disclosure of Illum, Illum (1986), Hanson or Salzman, alone or in combination.

For the foregoing reasons, Appellant submits that claims 1-28 should be allowed.

Respectfully submitted,



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Date: July 1, 1996

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APPENDIX A

Claims on Appeal

1. A particulate drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres and a systemically active drug, wherein at least 90 wt % of the microspheres of the composition have a diameter of between 0.1 μm and 10 μm, and wherein the composition is capable of systemic delivery of a therapeutically effective amount of the drug to a mammal upon intranasal administration.

2. A drug delivery composition according to Claim 1 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

3. A drug delivery composition according to Claim 1 or 2 wherein the microspheres comprise starch, gelatin, albumin, collagen, or dextran.

4. A drug delivery composition according to Claim 3 wherein the microspheres are starch microspheres.

5. A drug delivery composition according to Claim 1 wherein the microsphere material is cross-linked.

6. A drug delivery composition according to Claim 1 wherein the microspheres have been heated to stabilize the microspheres.

7. A drug delivery composition according to Claim 1 additionally comprising an absorption enhancer.

8. A drug delivery composition according to Claim 7 wherein the absorption enhancer is a surfactant.

9. A drug delivery composition according to Claim 1 wherein the drug is a biologically active peptide.

10. A drug delivery composition according to Claim 9 wherein the peptide is insulin or calcitonin.

11. A system for intranasal drug delivery comprising a drug delivery composition according to Claim 1 and a container having an orifice through which the composition can be delivered to the nasal mucosa in a gas stream.

12. A system according to Claim 11 wherein the system is such that, in use, the product of the flow rate and the square of the microsphere aerodynamic diameter is greater than 2000 μm^2.litres/min.

13. A method of delivering a drug to the nasal mucosa, comprising introducing a gas stream containing a composition according to Claim 1 into the nose.

14. A method of treating diabetes comprising introducing a gas stream containing a composition according to Claim 1 wherein the systemically active drug is insulin into the nose.

15. The drug delivery composition of claim 1 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

16. The drug delivery composition of claim 1 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.

17. A method for systemically delivering an active drug to a mammal, the method comprising:

a) providing a composition comprising a plurality of bioadhesive microspheres and an active drug, wherein at least 90 wt % of the microspheres in the composition have a diameter between 0.1 μm and 10 μm; and

b) administering the composition to a mammal intranasally thereby to systemically delivery a therapeutically effective amount of the drug to the mammal.

18. The method of claim 17 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

19. The method of claim 17 wherein the microspheres comprise a material selected from the group consisting of starch, gelatin, albumin, collagen and dextran.

20. The method of claim 19 wherein the microspheres comprise starch.

21. The method of claim 17 wherein the microsphere material is cross-linked prior to step b).

22. The method of claim 17 wherein the microspheres are heated to stabilize the microspheres prior to step b).

23. The method of claim 17 the composition provided in step a) further comprises an absorption enhancer.

24. The method of claim 23 wherein the absorption enhancer is a surfactant.

25. The method of claim 17 wherein the drug is a biologically active peptide.

26. The method of claim 25 wherein the peptide is insulin or calcitonin.

27. The method of claim 17 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

28. The method of claim 17 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.

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1. The obviousness-type double patenting rejection over U.S. Patent No. 5,204,108 should be withdrawn.
   a. U.S. Patent No. 5,204,108 to Illum
   b. Claims 1-10 and 15-16 of the present application
   c. The rejection does not meet the legal criteria defined by the courts.
2. The double patenting rejection over U.S. Patent No. 5,204,108 should be withdrawn.
   a. Claims 11-14 and 17-28 of the present application
   b. The rejection does not meet the legal criteria defined by the courts.
3. The claimed compositions and methods are not disclosed by Illum.
   a. U.S. Patent No. 4,487,091 to Illum.
   b. Nothing in Illum provides any disclosure or suggestion of the compositions or methods claimed by the Appellant.
   c. The rejection does not meet the legal criteria defined by the courts.
4. The claimed compositions and methods are not obvious in view of Illum (1986).
   a. Illum (1986).
   b. Illum (1986) does not disclose or suggest the drug delivery compositions or methods for their administration claimed.
   c. The rejection does not meet the legal criteria defined by the courts.
5. The claimed methods and compositions are not obvious in view of Illum or Illum 1986, alone or in view of Hanson or Salzman.
   a. The disclosure of the '091 patent to Illum and Illum (1986).
   b. The disclosure of Hanson and Salzman.
   c. In combination, Illum, Illum (1986), Hanson, and Salzman do not disclose or suggest the compositions and methods claimed.
   d. There would have been no motivation to make the claimed compositions or to practice the claimed methods in view of Illum, Illum (1986), Hanson or Salzman, alone or in combination.
   e. The unexpected results demonstrated by the Appellant are not obvious in view of Illum, Illum (1986), Hanson and Salzman.
   f. Summary

IX. Summary and Conclusion